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4/15/06

Mr. Anthony R. Brighton
101 Merrimac Street
Boston, Massachusetts 02114-4716

Re: Arthur Pernokas
SP02-1693

Dear Mr. Brighton,

My name is Joseph C. Bergeron Jr. MD. I am a licensed physician in the Commonwealth of Massachusetts and am board certified by the American Board of Pathology in Pathology (Anatomic and Clinical) and have added qualification in Cytopathology. I am a full-time practicing pathologist.
A current CV has been sent to you. I have not published in the past ten years.
My rate of compensation is $250.00 per hour for case and slide review plus mileage and other incidental costs. My compensation for court appearances is $450.00 per hour.
I have not testified at trial or by deposition in the past four years.

I have been asked to review slides at the Anna Jaques Hospital in Newburyport, MA and to respond to the questions of Marc B. Garnick MD. I have been asked to review the slides with Dr. Garnick after my initial review. I have been asked questions regarding the pathology specimen and findings on the slides.

In preparation for the review of the slides I reviewed:

1. Letter of Marc B. Garnick MD outlining questions regarding report SP02-1693.
2. 03/14/02 CT Report concerning Arthur Pernokas.
3. 03/14/02 History and Physical Examination, 03/19/02 Operative Report, and 03/23/02 Discharge Summary of Putnam Breed, MD, concerning Arthur Pernokas.
4. 03/22/02 Consultation Report of Paul Spieler MD.
5. Surgical Pathology Report and Laboratory Results, Specimen #SP02-1693.
6. Pertinent references in Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas (2004), a standard reference text.

I have reviewed the slides of the pathology specimen and discussed my findings with Dr. Garnick in the same way as I would with any treating physician or participant in a hospital tumor board or diagnostic conference.

My interpretations of the pathology report, microscopic sections and pathologic findings are based on my training, numerous courses and more than 20 years of clinical experience as a practicing pathologist dealing with colon cancer.

JCB

I reviewed 12 slides on this case at Anna Jaques Hospital on Friday 2/24/06 and again on 4/12/06. The review was done in the pathologist's office. The slides were returned to the lab personnel.

Answers to the questions posed by Dr. Garnick are:

1. According to the pathology report the tumor was 5 x 10.5 cm.

2. The sections examined represent a small sample of the entire lesion.
   The mucosal surface (digestive tract surface inside of the bowel) is ulcerated and has adjacent numerous small blood vessels and acute inflammation. There is some blood at the surface of the ulceration.
   The tumor is predominantly a moderately differentiated adenocarcinoma of the usual colonic type. There is an area of microglandular differentiation on slide B2. The microglandular pattern has been associated with high frequency microsatellite instability.
   The deep aspect of the tumor has a mucinous component as does the tumor in the lymph nodes on slides B9 and B10. Slide B9 also has an area of perinodal involvement by mucinous colonic adenocarcinoma.
   A small cell component is not identified.

3. In the slides examined I did not see a pre-existing adenoma. This may be due to sampling or due to de novo cancer without a pre-existing adenoma.

4. Lymphatic invasion is known by the nodal involvement. I did not discern vascular invasion although this was carefully and specifically searched for in the examinations of the slides. No special stains were performed on this tumor.

5. The tumor did extend through the muscularis propria into non-peritoneal adipose tissue (the local fatty tissue immediately adjacent to the tumor in the bowel) rendering this a T3 lesion. I did not see tumor at the peritoneal serosal surface (the abdominal cavity) on the sections examined and the initial pathologic examination did not identify involvement of the abdominal cavity.
   The surgical margins of the bowel and appendix do not contain tumor.

6. I cannot tell whether all lymph nodes in the resection were examined, but finding 12-14 lymph nodes is generally considered adequate for staging. Fourteen lymph nodes were found. Three of the 14 lymph nodes do contain tumor. The three involved nodes measure 0.5cm, 0.5cm and 1.0cm in diameter. The involved nodes do have extra nodal tumor extension. These nodes ordinarily would have been found in close proximity and adjacent to the tumor in the bowel. None of the eleven uninvolved negative for tumor lymph nodes contain small clusters of tumor less than 2 millimeters in diameter (micrometastases) and these would be nodes further away from the bowel tumor. The tumor in the involved nodes is easily identified and consists of aggregates of cells or pools of mucin of such a size that an experienced pathologist may grossly identify the tumor with naked eyes without a microscope at the time of the initial pathologic examination.

JWB

7. Perhaps the blocks or unstained slides from the blocks could be requested. The facility did not want to release the original slides.

8. The ulcerated mucosal surface would have caused blood loss and there is some microscopic blood at the digestive tract surface of the bowel. From the slides and gross description I cannot assess the volume of blood loss or whether there was an acute massive bleeding episode. The pathologist did not describe whether the contents of the bowel contained blood.

9. Stains for MSI-H could be done on slide B9. The mucinous component and the microglandular differentiation have been associated with a hereditary type of colon cancer or HNPCC. This type of cancer occurs at an earlier age.

10. When I was at the hospital I did not ask whether the gross specimen was available. It generally would not be available at this late date.

Sincerely yours,

Joseph C. Bergeron MD

To: Attys. Anthony Brighton and Charles Reidy III
From: Marc B. Garnick MD
Re: Points to consider re **Pernokas v Paster** in requesting outside review with expert pathologist
Date: 23 January 2006

Attys. Brighton and Reidy:

As discussed today in a teleconference with Atty. Brighton, and as requested, I have reviewed the pathology report accompanying the medical records of Pernokas v Paster (Pathology report SP02-1693). I would be most interested in an outside expert interpretation of the pathology with the following points to consider. *(Please note that the line of my questions listed below are purely for informational content and fact gathering, without any regard (at this time) to interpretation or expert opinion formation.)*
Referring to the **Pathology report SP02-1693:**

1. What is size of the lesion?
2. Is there agreement on the degree of differentiation? If not, what is the expert's interpretation? Were there areas of poorly differentiated or undifferentiated tumor? Was there any evidence of signet ring cell or mucinous carcinoma present? I assume there was no small cell component but please confirm.
1. Is there comment on whether the cancer arose from an adenoma? If so, how is this determined?
2. What is the status of the presence or absence of vascular and/or lymphatic invasion? Were special stains performed to identify the presence of vascular/lymphatic channels inn order to determine this finding?
3. Is there agreement on the depth of microscopic invasion through the muscularis propria and into pericolonic adipose tissue, rendering this a T3 lesion?
4. How many lymph nodes were actually contained and how many were examined? What is the expert's opinion on assessing the prognostic variables regarding number of nodes necessary to evaluate in patients with T3 lesions especially in light of the College of American Pathologist's consensus criteria? (CAP; *Arch Pathol Lab Med* 2000;124:979** -- *see attached below*)
5. Are the blocks available, and if so, are there additional studies/cuts necessary to help answer the above queries?
6. Was there any evidence of active hemorrhage from the gross appearance of the tumor, if such a specimen is available for review?
7. Are there additional pathologic/molecular factors that an expert pathologist would want to consider or evaluate (eg criteria from CAP) that would shed light to help explain the biological behaviour of this cancer?

As discussed, I would like to review the pathology specimen from the original resection and if additional questions arise from that review that need clarification/insight from your expert pathologist, I will issue another memo.

Attys. Anthony Brighton and Charles Reidy III
Marc B. Garnick MD
Points to consider re **Pernokas v Paster**

Marc B. Garnick MD

Abstract of citation cited above:

***Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, Hammond ME, Henson DE, Hutter RV, Nagle RB, Nielsen ML, Sargent DJ, Taylor CR, Welton M, Willett C.Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med. 2000 Jul;124(7):979-94.*

BACKGROUND: Under the auspices of the College of American Pathologists, the current state of knowledge regarding pathologic prognostic factors (factors linked to outcome) and predictive factors (factors predicting response to therapy) in colorectal carcinoma was evaluated. A multidisciplinary group of clinical (including the disciplines of medical oncology, surgical oncology, and radiation oncology), pathologic, and statistical experts in colorectal cancer reviewed all relevant medical literature and stratified the reported prognostic factors into categories that reflected the strength of the published evidence demonstrating their prognostic value. Accordingly, the following categories of prognostic factors were defined. Category I includes factors definitively proven to be of prognostic import based on evidence from multiple statistically robust published trials and generally used in patient management. Category IIA includes factors extensively studied biologically and/or clinically and repeatedly shown to have prognostic value for outcome and/or predictive value for therapy that is of sufficient import to be included in the pathology report but that remains to be validated in statistically robust studies. Category IIB includes factors shown to be promising in multiple studies but lacking sufficient data for inclusion in category I or IIA. Category III includes factors not yet sufficiently studied to determine their prognostic value. Category IV includes factors well studied and shown to have no prognostic significance. MATERIALS AND METHODS: The medical literature was critically reviewed, and the analysis revealed specific points of variability in approach that prevented direct comparisons among published studies and compromised the quality of the collective data. Categories of variability recognized included the following: (1) methods of analysis, (2) interpretation of findings, (3) reporting of data, and (4) statistical evaluation. Additional points of variability within these categories were defined from the collective experience of the group. Reasons for the assignment of an individual prognostic factor to category I, II, III, or IV (categories defined by the level of scientific validation) were outlined with reference to the specific types of variability associated with the supportive data. For each factor and category of variability related to that factor, detailed recommendations for improvement were made. The recommendations were based on the following aims: (1) to increase the uniformity and completeness of pathologic evaluation of tumor specimens, (2) to enhance the quality of the data needed for definitive evaluation of the prognostic value of individual prognostic factors, and (3) ultimately, to improve patient care. RESULTS AND CONCLUSIONS: Factors that were determined to merit inclusion in

category I were as follows: the local extent of tumor assessed pathologically (the pT category of the TNM staging system of the American Joint Committee on Cancer and the Union Internationale Contre le Cancer [AJCC/UICC]); regional lymph node metastasis (the pN category of the TNM staging system); blood or lymphatic vessel invasion; residual tumor following surgery with curative intent (the R classification of the AJCC/UICC staging system), especially as it relates to positive surgical margins; and preoperative elevation of carcinoembryonic antigen elevation (a factor established by laboratory medicine methods rather than anatomic pathology). Factors in category IIA included the following: tumor grade, radial margin status (for resection specimens with nonperitonealized surfaces), and residual tumor in the resection specimen following neoadjuvant therapy (the ypTNM category of the TNM staging system of the AJCC/UICC).